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NEWS 6 Apr 23 PRE-1967 REFERENCES NOW SEARCHABLE IN CAPLUS AND CA

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CURRENT MACINTOSH VERSION IS V5.0C (ENG) AND V5.0JB (JP),
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COPYRIGHT (C) 2001 Cambridge Scientific Abstracts (CSA)

=> s ((myocardial failure) or (myocardial hypertrophy)(50a)(treatment))
L1 1956 ((MYOCARDIAL FAILURE) OR (MYOCARDIAL HYPERTROPHY)(50A)(TREATMENT
))

=> s ((alpha myosin heavy chain) or (alpha-MHC))
L2 1766 ((ALPHA MYOSIN HEAVY CHAIN) OR (ALPHA-MHC))

=> s l1 and l2
L3 11 L1 AND L2

=> dup rem l3
PROCESSING COMPLETED FOR L3
L4 5 DUP REM L3 (6 DUPLICATES REMOVED)

=> d l4 1-5 ibib abs

L4 ANSWER 1 OF 5 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 1
ACCESSION NUMBER: 2000284736 EMBASE
TITLE: Modulation of in vivo cardiac hypertrophy with insulin-like growth factor-1 and angiotensin-converting enzyme inhibitor: Relationship between change in myosin isoform and progression of left ventricular dysfunction.
AUTHOR: Iwanaga Y.; Kihara Y.; Yoneda T.; Aoyama T.; Sasayama S.
CORPORATE SOURCE: Dr. Y. Kihara, Dept. of Cardiovascular Medicine, Kyoto
Univ. Grad. School of Medicine, 54 Shogoin Kawaharacho, Sakyo-ku, Kyoto 606-8507, Japan. kihara@kuhp.kyoto-u.ac.jp
SOURCE: Journal of the American College of Cardiology, (2000) 36/2
(635-642).
Refs: 46
ISSN: 0735-1097 CODEN: JACCDI
PUBLISHER IDENT.: S 0735-1097(00)00769-5
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Objectives. Supplemental **myocardial hypertrophy** induced by insulin-like growth factor (IGF)-1 may prevent transition from hypertrophy to heart failure under chronic mechanical overload. Background. Several studies have suggested that IGF-1 **treatment** may be beneficial in chronic heart failure. In addition, recent studies indicated that the amount of a-myosin heavy chain (MHC) plays a significant hemodynamic role in large animals including humans. Methods. We treated Dahl salt-sensitive hypertensive rats on a long-term basis with IGF-1. The effects were compared with those produced by treatment using a sub-antihypertensive dose of temocapril, an angiotensin-converting enzyme (ACE) inhibitor. At 11 weeks, when these rats displayed compensated left ventricular hypertrophy (LVH), they were randomized to three groups: 1) IGF group (3 mg/kg/day); 2) temocapril group (1 mg/kg/day); and 3) vehicle (control) group. Results. After 15 weeks, the control rats showed left ventricular (LV) enlargement and severe LV dysfunction and rapidly died of pulmonary congestion (mean survival time: 16.8 .+-. 0.5 weeks). The survival time was significantly shortened (15.6 .+-. 0.3 weeks) in the IGF-1 group but significantly prolonged (19.5 .+-. 0.6 weeks) in the temocapril group. The rats in the IGF-1 group showed accelerated LV dilation and dysfunction. Of the several parameters investigated, it was found that the relative amounts of MHC isoforms differed among the three groups. The **.alpha.-MHC** mRNA level was decreased by 52% ($p < 0.01$) in the IGF group, while it increased by 58% ($p < 0.01$) in the temocapril group compared with the control group. These changes were related to the progression of LV dysfunction. Conclusions. Supplemental **myocardial hypertrophy** with long-term IGF-1 **treatment** may not be beneficial if concentric LVH already exists. Our data suggest that IGF-1 may not protect myocardial performance when its hypertrophic effect aggravates the reduction of **.alpha.-MHC**. By contrast, the ACE inhibitor may improve myocardial function and prognosis by preventing the down-regulation of this isoform.

L4 ANSWER 2 OF 5 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:96374 CAPLUS
DOCUMENT NUMBER: 130:152121
TITLE: Intracellular inhibitors of Gq protein signaling and their role in the control of myocardial hypertrophy
INVENTOR(S): Koch, Walter J.; Lefkowitz, Robert J.; Akhter, Shahab A.; Luttrell, Louis M.
PATENT ASSIGNEE(S): Duke University, USA
SOURCE: PCT Int. Appl., 44 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9905294	A1	19990204	WO 1998-US15152	19980724

W: AU, CA, JP
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE

AU 9885793	A1	19990216	AU 1998-85793	19980724
EP 1012313	A1	20000628	EP 1998-936973	19980724

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI

PRIORITY APPLN. INFO.: US 1997-53659 P 19970724
WO 1998-US15152 W 19980724

AB Methods of preventing or limiting myocardial hypertrophy by inhibiting Gq-coupled receptor signaling in myocardial tissue are described. In particular, a C-terminal peptide of the .alpha. subunit of Gq is shown to inhibit Gq signalling and to block hypertrophy-assocd. events in animal cell culture and in transgenic animals. Transgenic mice expressing a gene for the C-terminal peptide (305-359) of the Gq .alpha. subunit using the myocardium-specific .**alpha.-myosin heavy chain** gene were prepd. by std. methods. In these mice, the p24/p44 MAP kinase activity in the myocardium was induced 1.3-fold by angiotensin II and endothelin I. In control mice, kinase induction was .apprx.4-fold. The effect was specific for Gq-coupled receptors as the peptide did not affect basal or .beta.2-adrenoceptor-mediated increases in adenyl cyclase activity. The transgenic mice were also resistant to pressure overload hypertrophy brought on by surgical transverse aortic constriction.

REFERENCE COUNT: 6
REFERENCE(S): (1) Akhter; Science 1998, V280, P574 CAPLUS
(2) D'Angelo; Proc Natl Acad Sci USA 1997, V94, P8121 CAPLUS
(3) Lamorte; J Biol Chem 1994, V269(18), P13490 CAPLUS
(4) Meij, J; Molec and Cellular Biochem 1996, V157, P31 CAPLUS
(5) Sah; J Biol Chem 1996, V271(49), P31185 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 3 OF 5 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:543192 CAPLUS
DOCUMENT NUMBER: 129:171486
TITLE: Diagnosis and treatment of **myocardial failure** associated with expression of .alpha.- and .beta.-myosin heavy chains
INVENTOR(S): Bristow, Michael R.; Leinwand, Leslie A.; Minobe, Wayne; Nakao, Koichi
PATENT ASSIGNEE(S): University Technology Corporation, USA
SOURCE: PCT Int. Appl., 48 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9833942	A1	19980806	WO 1998-US1983	19980130

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG

AU 9861410	A1	19980825	AU 1998-61410	19980130
EP 1012329	A1	20000628	EP 1998-906089	19980130

R: BE, CH, DE, ES, FR, GB, IT, LI, NL, SE, IE

PRIORITY APPLN. INFO.: US 1997-36987 P 19970130
US 1997-38911 P 19970226
WO 1998-US1983 W 19980130

AB Disclosed is a method for the diagnosis of human **myocardial failure** by quantitating the expression of .**alpha.-myosin heavy chain** (.**alpha.-MHC**), .beta.-myosin heavy chain (.beta.-MHC), or both in a left ventricular myocardial sample with the PCR method. Since the decrease in .**alpha.-MHC** and increase in .beta.-MHC gene expression have been known to be assocd. with aging and thus **myocardial failure**, myocardial function may be improved by up-regulation of .**alpha.-MHC** or down-regulation of .beta.-MHC.

L4 ANSWER 4 OF 5 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 2
ACCESSION NUMBER: 97361878 EMBASE
DOCUMENT NUMBER: 1997361878
TITLE: Changes in gene expression in the intact human heart: Downregulation of .**alpha.-myosin heavy chain** in hypertrophied, failing ventricular myocardium.
AUTHOR: Lowes B.D.; Minobe W.; Abraham W.T.; Rizeq M.N.; Bohlmeyer T.J.; Quaife R.A.; Roden R.L.; Dutcher D.L.; Robertson A.D.; Voelkel N.F.; Badesch D.B.; Groves B.M.; Gilbert E.M.; Bristow M.R.
CORPORATE SOURCE: Dr. M.R. Bristow, Division of Cardiology, Univ. of Colorado Hlth. Sci. Center, Campus Box B139, 4200 East 9th Avenue, Denver, CO 80262, United States.
Michael.Bristow@UCHSC.edu
SOURCE: Journal of Clinical Investigation, (1997) 100/9 (2315-2324).
Refs: 67
ISSN: 0021-9738 CODEN: JCINAO
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
018 Cardiovascular Diseases and Cardiovascular Surgery
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Using quantitative RT-PCR in RNA from right ventricular (RV) endomyocardial biopsies from intact nonfailing hearts, and subjects with moderate RV failure from primary pulmonary hypertension (PPH) or idiopathic dilated cardiomyopathy (IDC), we measured expression of genes involved in regulation of contractility or hypertrophy. Gene expression was also assessed in LV (left ventricular) and RV free wall and RV endomyocardium of hearts from end-stage IDC subjects undergoing heart transplantation or from nonfailing donors. In intact failing hearts, downregulation of .beta.1-receptor mRNA and protein, upregulation of atrial natriuretic peptide mRNA expression, and increased myocyte diameter indicated similar degrees of failure and hypertrophy in the IDC and PPH phenotypes. The only molecular phenotypic difference between PPH and IDC RVs was upregulation of .beta.2-receptor gene expression in PPH but not IDC. The major new findings were that (a) both nonfailing intact and explanted human ventricular myocardium expressed substantial amounts of .**alpha.-myosin heavy chain** mRNA (.**alpha.-MHC**, 23-34% of total), and (b) in heart failure .**alpha.-MHC** was down-regulated (by 67-84%) and .beta.-MHC gene expression was up-regulated. We conclude that at the mRNA level nonfailing human heart expresses substantial .**alpha.-MHC**. In **myocardial failure** this alteration in gene expression of MHC isoforms, if translated into protein expression, would decrease myosin ATPase enzyme velocity and slow speed of contraction.

L4 ANSWER 5 OF 5 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1998:51971 BIOSIS
DOCUMENT NUMBER: PREV199800051971
TITLE: Captopril modifies gene expression in hypertrophied and failing hearts of aged spontaneously hypertensive rats.
AUTHOR(S): Brooks, Wesley W. (1); Bing, Oscar H. L.; Conrad, Chester H.; O'Neill, Lydia; Crow, Michael T.; Lakatta, Edward G.; Dostal, David E.; Baker, Kenneth M.; Boluyt, Marvin O.
CORPORATE SOURCE: (1) Res. Serv., Boston VA Med. Cent., 150 S. Huntington Ave., Boston, MA 02130 USA
SOURCE: Hypertension (Dallas), (Dec., 1997) Vol. 30, No. 6, pp. 1362-1368.
ISSN: 0194-911X.
DOCUMENT TYPE: Article
LANGUAGE: English

AB The spontaneously hypertensive rat (SHR) exhibits a transition from stable compensated left ventricular (LV) hypertrophy to heart failure (HF) at a mean age of 21 months that is characterized by a decrease in **alpha-myosin heavy chain** (a-MHC) gene expression and increases in the expression of the atrial natriuretic factor (ANF),

pro-alpha1(III) collagen, and transforming growth factor beta1 (TGF-beta1) genes. We tested the hypotheses that angiotensin-converting enzyme inhibition (ACEI) in SHR would prevent and reverse HF-associated changes in gene expression when administered prior to and after the onset of HF, respectively. We also investigated the effect of ACEI on circulating and cardiac components of the renin-angiotensin system. ACEI (captopril 2 g/L in the drinking water) was initiated at 12, 18, and 21 months of age in SHR without HF and in SHR with HF. Results were compared with those of age-matched normortensive Wistar-Kyoto (WKY) rats, and to untreated SHR with and without evidence of HF. ACEI initiated prior to failure prevented the changes in **alpha-MHC**, ANF, pro-alpha1,(III) collagen, and TGF-beta1 gene expression that are associated with the transition to HF. ACEI initiated after the onset of HF lowered levels of TGF-beta1 mRNA by 50% (P<.05) and elevated levels of **alpha-MHC** mRNA two- to threefold (P<.05). Circulating levels of renin and angiotensin I were elevated four- to sixfold by ACEI, but surprisingly, plasma levels of angiotensin II were not reduced. ACEI increased LV renin mRNA levels in WKY and SHR by two- to threefold but did not influence LV levels of angiotensinogen mRNA. The results suggest that the anti-HF benefits of ACEI in SHR may be mediated, at least in part, by effects on the expression of specific genes, including those encoding **alpha-MHC**, ANF, TGF-beta1, pro-alpha1(III) collagen, and renin-angiotensin system components.

=> d his

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FILE 'EMBASE, BIOSIS, MEDLINE, CAPLUS, LIFESCI' ENTERED AT 16:51:48 ON 30 APR 2001

L1 1956 S ((MYOCARDIAL FAILURE) OR (MYOCARDIAL HYPERTROPHY)(50A)(TREATM
L2 1766 S ((ALPHA MYOSIN HEAVY CHAIN) OR (ALPHA-MHC))
L3 11 S L1 AND L2
L4 5 DUP REM L3 (6 DUPLICATES REMOVED)

=> s (myocardial failure) or (myocardial hypertrophy)
L5 6243 (MYOCARDIAL FAILURE) OR (MYOCARDIAL HYPERTROPHY)

=> s l2 and l5
L6 29 L2 AND L5

=> dup rem l6
PROCESSING COMPLETED FOR L6
L7 14 DUP REM L6 (15 DUPLICATES REMOVED)

=> d l7 1-14 ibib abs

L7 ANSWER 1 OF 14 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 1
ACCESSION NUMBER: 2000284736 EMBASE
TITLE: Modulation of in vivo cardiac hypertrophy with insulin-like growth factor-1 and angiotensin-converting enzyme inhibitor: Relationship between change in myosin isoform and progression of left ventricular dysfunction.
AUTHOR: Iwanaga Y.; Kihara Y.; Yoneda T.; Aoyama T.; Sasayama S.
CORPORATE SOURCE: Dr. Y. Kihara, Dept. of Cardiovascular Medicine, Kyoto Univ. Grad. School of Medicine, 54 Shogoin Kawaharacho, Sakyo-ku, Kyoto 606-8507, Japan. kihara@kuhp.kyoto-u.ac.jp
SOURCE: Journal of the American College of Cardiology, (2000) 36/2 (635-642).
Refs: 46
ISSN: 0735-1097 CODEN: JACCDI
PUBLISHER IDENT.: S 0735-1097(00)00769-5
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Objectives. Supplemental **myocardial hypertrophy** induced by insulin-like growth factor (IGF)-1 may prevent transition from hypertrophy to heart failure under chronic mechanical overload. Background. Several studies have suggested that IGF-1 treatment may be beneficial in chronic heart failure. In addition, recent studies indicated that the amount of a-myosin heavy chain (MHC) plays a significant hemodynamic role in large animals including humans. Methods. We treated Dahl salt-sensitive hypertensive rats on a long-term basis with IGF-1. The effects were compared with those produced by treatment using a sub-antihypertensive dose of temocapril, an angiotensin-converting enzyme (ACE) inhibitor. At 11 weeks, when these rats displayed compensated left ventricular hypertrophy (LVH), they were randomized to three groups: 1) IGF group (3 mg/kg/day); 2) temocapril group (1 mg/kg/day); and 3) vehicle (control) group. Results. After 15 weeks, the control rats showed left ventricular (LV) enlargement and severe LV dysfunction and rapidly died of pulmonary congestion (mean survival time: 16.8 .+-. 0.5 weeks). The survival time was significantly shortened (15.6 .+-. 0.3 weeks) in the IGF-1 group but significantly prolonged (19.5 .+-. 0.6 weeks) in the temocapril group. The rats in the IGF-1 group showed accelerated LV dilation and dysfunction. Of the several parameters investigated, it was found that the relative amounts of MHC isoforms differed among the three groups. The .**alpha.-MHC** mRNA level was decreased by 52% ($p < 0.01$) in the IGF group, while it increased by 58% ($p < 0.01$) in the temocapril group compared with the control group. These changes were related to the progression of LV dysfunction. Conclusions. Supplemental **myocardial hypertrophy** with long-term IGF-1 treatment may not be beneficial if concentric LVH already exists. Our data suggest that IGF-1 may not protect myocardial performance when its hypertrophic effect aggravates the reduction of .**alpha.-MHC**. By contrast, the ACE inhibitor may improve myocardial function and prognosis by preventing the down-regulation of this isoform. (C) 2000 by the American College of Cardiology.

L7 ANSWER 2 OF 14 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 2000:385087 BIOSIS
DOCUMENT NUMBER: PREV200000385087
TITLE: beta2-adrenergic receptor overexpression driven by **alpha-MHC** promoter is downregulated in hypertrophied and failing myocardium.
AUTHOR(S): Sheridan, Desmond J.; Autelitano, Dominic J.; Wang, Binghui; Percy, Elodie; Woodcock, Elizabeth A.; Du, Xiao-Jun (1)
CORPORATE SOURCE: (1) Baker Medical Research Institute, St. Kilda Road Central, Melbourne, Victoria, 8008 Australia
SOURCE: Cardiovascular Research, (July, 2000) Vol. 47, No. 1, pp. 133-141. print.
ISSN: 0008-6363.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Objective: The **alpha-myosin heavy chain (alpha-MHC)** promoter is frequently used to direct cardiac specific transgene expression. We studied whether transgene expression controlled by this promoter was altered under conditions of cardiac hypertrophy and failure. Methods: Transgenic (TG) mice overexpressing human beta2-adrenergic receptors (beta2AR) and wild type (WT) controls were subjected to thoracic aortic constriction (TAC) or sham operation and studied at 1, 3 and 8 weeks after surgery. Results: Sham operated TG mice had higher heart rates and left ventricular (LV) contractility than WT (all $P < 0.01$), demonstrating enhanced betaAR activation. TAC at 1, 3 and 8 weeks produced progressive LV hypertrophy which was similar between WT and TG mice. Evidence of heart failure was more marked in TG mice with a greater increase in weights of the right ventricle and lungs and a higher prevalence of atrial thrombus ($P < 0.05$ in each case). In hypertrophied TG hearts, endogenous **alpha-MHC** mRNA transcripts in LV were maintained at 1 and 3 weeks, but were reduced by approximately 40% relative to the sham-operated group at 8 weeks after TAC. Transgene expression, measured as human beta2AR mRNA, was

reduced by 45% at 1 and 3 weeks and by 70% at 8 weeks after TAC. beta2AR binding sites were reduced by 35, 47 and 65%, respectively, at 1, 3 and 8 weeks. Conclusion: Cardiac hypertrophy and failure cause downregulation of the endogenous **alpha-MHC** as well as cardiac specific overexpression of the transgene directed by an **alpha-MHC** promoter.

L7 ANSWER 3 OF 14 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:96374 CAPLUS
DOCUMENT NUMBER: 130:152121
TITLE: Intracellular inhibitors of Gq protein signaling and their role in the control of **myocardial hypertrophy**
INVENTOR(S): Koch, Walter J.; Lefkowitz, Robert J.; Akhter, Shahab A.; Luttrell, Louis M.
PATENT ASSIGNEE(S): Duke University, USA
SOURCE: PCT Int. Appl., 44 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9905294	A1	19990204	WO 1998-US15152	19980724
W: AU, CA, JP				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9885793	A1	19990216	AU 1998-85793	19980724
EP 1012313	A1	20000628	EP 1998-936973	19980724
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				

PRIORITY APPLN. INFO.: US 1997-53659 P 19970724
WO 1998-US15152 W 19980724

AB Methods of preventing or limiting **myocardial hypertrophy** by inhibiting Gq-coupled receptor signaling in myocardial tissue are described. In particular, a C-terminal peptide of the .alpha. subunit of Gq is shown to inhibit Gq signalling and to block hypertrophy-assocd. events in animal cell culture and in transgenic animals. Transgenic mice expressing a gene for the C-terminal peptide (305-359) of the Gq .alpha. subunit using the myocardium-specific **.alpha.-myosin heavy chain** gene were prepd. by std. methods. In these mice, the p24/p44 MAP kinase activity in the myocardium was induced 1.3-fold by angiotensin II and endothelin I. In control mice, kinase induction was .apprx.4-fold. The effect was specific for Gq-coupled receptors as the peptide did not affect basal or .beta.2-adrenoceptor-mediated increases in adenyl cyclase activity. The transgenic mice were also resistant to pressure overload hypertrophy brought on by surgical transverse aortic constriction.

REFERENCE COUNT: 6
REFERENCE(S): (1) Akhter; Science 1998, V280, P574 CAPLUS
(2) D'Angelo; Proc Natl Acad Sci USA 1997, V94, P8121 CAPLUS
(3) Lamorte; J Biol Chem 1994, V269(18), P13490 CAPLUS
(4) Meij, J; Molec and Cellular Biochem 1996, V157, P31 CAPLUS
(5) Sah; J Biol Chem 1996, V271(49), P31185 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 4 OF 14 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:543192 CAPLUS
DOCUMENT NUMBER: 129:171486
TITLE: Diagnosis and treatment of **myocardial failure** associated with expression of .alpha.- and .beta.-myosin heavy chains
INVENTOR(S): Bristow, Michael R.; Leinwand, Leslie A.; Minobe, Wayne; Nakao, Koichi
PATENT ASSIGNEE(S): University Technology Corporation, USA
SOURCE: PCT Int. Appl., 48 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9833942	A1	19980806	WO 1998-US1983	19980130
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9861410	A1	19980825	AU 1998-61410	19980130
EP 1012329	A1	20000628	EP 1998-906089	19980130
R: BE, CH, DE, ES, FR, GB, IT, LI, NL, SE, IE				

PRIORITY APPLN. INFO.: US 1997-36987 P 19970130
US 1997-38911 P 19970226
WO 1998-US1983 W 19980130

AB Disclosed is a method for the diagnosis of human **myocardial failure** by quantitating the expression of **.alpha.-myosin heavy chain** (**.alpha.-**MHC), .beta.-myosin heavy chain (.beta.-MHC), or both in a left ventricular myocardial sample with the PCR method. Since the decrease in **.alpha.-MHC** and increase in .beta.-MHC gene expression have been known to be assocd. with aging and thus **myocardial failure**, myocardial function may be improved by up-regulation of **.alpha.-MHC** or down-regulation of .beta.-MHC.

L7 ANSWER 5 OF 14 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1999:34338 BIOSIS
DOCUMENT NUMBER: PREV199900034338
TITLE: Cardiac specific overexpression of angiotensin converting enzyme in transgenic mice.
AUTHOR(S): Schwartz, Steven M. (1); Osinska, Hanna (1); Setser, Elizabeth A. (1); Akanbi, Adebola (1); Klevitsky, Raisa (1); Davis, Michael G.; Dorn, Gerald W., II; Nelson, David P.; Robbins, Jeffrey
CORPORATE SOURCE: (1) Child. Hosp. Med. Cent., Cincinnati, OH USA
SOURCE: Circulation, (Oct. 27, 1998) Vol. 98, No. 17 SUPPL., pp. 1346.
Meeting Info.: 71st Scientific Sessions of the American Heart Association Dallas, Texas, USA November 8-11, 1998 The American Heart Association
. ISSN: 0009-7322.
DOCUMENT TYPE: Conference
LANGUAGE: English

L7 ANSWER 6 OF 14 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 2
ACCESSION NUMBER: 97268450 EMBASE
DOCUMENT NUMBER: 1997268450
TITLE: Transgenic mice with cardiac overexpression of .alpha.(1B)-adrenergic receptors. In vivo .alpha.1-adrenergic receptor-mediated regulation of .beta.-adrenergic signaling.
AUTHOR: Akhter S.A.; Milano C.A.; Shotwell K.F.; Cho M.-C.; Rockman H.A.; Lefkowitz R.J.; Koch W.J.
CORPORATE SOURCE: W.J. Koch, Dept. of Surgery, Duke University Medical Center, P. O. Box 2606, Durham, NC 27710, United States
SOURCE: Journal of Biological Chemistry, (1997) 272/34 (21253-21259).
Refs: 29
ISSN: 0021-9258 CODEN: JBCHA3
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Transgenic mice were generated with cardiac-specific overexpression of the wild-type (WT) .alpha.(1B)-adrenergic receptor (AR) using the murine **.alpha.- myosin heavy chain** gene promoter. Previously, we described transgenic mice with **.alpha.-myosin heavy chain**-directed expression of a constitutively active mutant .alpha.(1B)-AR that had a phenotype of **myocardial hypertrophy** (Milano, C. A., Dolber, P. C., Rockman, H. A., Bond, R. A., Venable M. E., Allen, L. F., and Lefkowitz, R. J. (1994) Proc. Natl. Acad. Sci. U.S.A. 91, 10109-10113). In animals with >40-fold WT .alpha.1-AR overexpression, basal myocardial diacylglycerol content was significantly increased, indicating enhanced .alpha.1- adrenergic signaling and phospholipase C activity. In contrast to the mice overexpressing constitutively active mutant .alpha.(1B)-ARs,

the hearts of these mice did not develop cardiac hypertrophy despite an 8-fold increase in ventricular mRNA for atrial natriuretic factor. In vivo physiology was studied in anesthetized intact animals and showed left ventricular contractility in response to the .beta.-agonist isoproterenol to be significantly depressed in animals overexpressing WT .alpha.(1B)ARs.
Membranes purified from the hearts of WT .alpha.(1B)AR-overexpressing mice
demonstrated significantly attenuated adenylyl cyclase activity basally and after stimulation with isoproterenol, norepinephrine, or phenylephrine. Interestingly, these in vitro changes in signaling were reversed after treating the mice with pertussis toxin, suggesting that the extraordinarily high levels of WT .alpha.(1B)-ARs can lead to coupling to pertussis toxin-sensitive G proteins. Another potential contributor to the observed decreased myocardial signaling and function could be enhanced
.beta.-AR desensitization as .beta.-adrenergic receptor kinase (.beta.ARK1) activity was found to be significantly elevated (>3- fold) in myocardial extracts isolated from WT .alpha.(1B)-AR-overexpressing mice.
This type of altered signal transduction may become critical in disease conditions such as heart failure where .beta.ARK1 levels are elevated and
.beta.-ARs are down-regulated, leading to a higher percentage of cardiac
.alpha.1ARs. Thus, these mice serve as a unique experimental model to study the in vivo interactions between .alpha.- and .beta.-ARs in the heart.

L7 ANSWER 7 OF 14 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 3
ACCESSION NUMBER: 97361878 EMBASE
DOCUMENT NUMBER: 1997361878
TITLE: Changes in gene expression in the intact human heart: Downregulation of **.alpha.-myosin heavy chain** in hypertrophied, failing ventricular myocardium.
AUTHOR: Lowes B.D.; Minobe W.; Abraham W.T.; Rizeq M.N.; Bohlmeyer T.J.; Quaife R.A.; Roden R.L.; Dutcher D.L.; Robertson A.D.; Voelkel N.F.; Badesch D.B.; Groves B.M.; Gilbert E.M.; Bristow M.R.
CORPORATE SOURCE: Dr. M.R. Bristow, Division of Cardiology, Univ. of Colorado Hlth. Sci. Center, Campus Box B139, 4200 East 9th Avenue, Denver, CO 80262, United States.
Michael.Bristow@UCHSC.edu
SOURCE: Journal of Clinical Investigation, (1997) 100/9 (2315-2324).
Refs: 67
ISSN: 0021-9738 CODEN: JCINAO
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
018 Cardiovascular Diseases and Cardiovascular Surgery
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Using quantitative RT-PCR in RNA from right ventricular (RV) endomyocardial biopsies from intact nonfailing hearts, and subjects with moderate RV failure from primary pulmonary hypertension (PPH) or idiopathic dilated cardiomyopathy (IDC), we measured expression of genes
involved in regulation of contractility or hypertrophy. Gene expression was also assessed in LV (left ventricular) and RV free wall and RV endomyocardium of hearts from end-stage IDC subjects undergoing heart
transplantation or from nonfailing donors. In intact failing hearts, downregulation of .beta.1-receptor mRNA and protein, upregulation of atrial natriuretic peptide mRNA expression, and increased myocyte diameter
indicated similar degrees of failure and hypertrophy in the IDC and PPH phenotypes. The only molecular phenotypic difference between PPH and IDC
RVs was upregulation of .beta.2-receptor gene expression in PPH but not
IDC. The major new findings were that (a) both nonfailing intact and explanted human ventricular myocardium expressed substantial amounts of .
alpha.-myosin heavy chain mRNA (.
alpha.-MHC, 23-34% of total), and (b) in heart failure .
alpha.-MHC was down-regulated (by 67-84%) and .beta.-MHC gene expression was up-regulated. We conclude that at the mRNA level nonfailing human heart expresses substantial **.alpha.-MHC**
. In **myocardial failure** this alteration in gene expression of MHC isoforms, if translated into protein expression, would decrease myosin ATPase enzyme velocity and slow speed of contraction.

L7 ANSWER 8 OF 14 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1998:51971 BIOSIS
DOCUMENT NUMBER: PREV199800051971
TITLE: Captopril modifies gene expression in hypertrophied and failing hearts of aged spontaneously hypertensive rats.
AUTHOR(S): Brooks, Wesley W. (1); Bing, Oscar H. L.; Conrad, Chester H.; O'Neill, Lydia; Crow, Michael T.; Lakatta, Edward G.; Dostal, David E.; Baker, Kenneth M.; Boluyt, Marvin O.
CORPORATE SOURCE: (1) Res. Serv., Boston VA Med. Cent., 150 S. Huntington Ave., Boston, MA 02130 USA
SOURCE: Hypertension (Dallas), (Dec., 1997) Vol. 30, No. 6, pp. 1362-1368.
ISSN: 0194-911X.
DOCUMENT TYPE: Article
LANGUAGE: English
AB The spontaneously hypertensive rat (SHR) exhibits a transition from stable
compensated left ventricular (LV) hypertrophy to heart failure (HF) at a mean age of 21 months that is characterized by a decrease in **alpha -myosin heavy chain** (a-MHC) gene expression
and increases in the expression of the atrial natriuretic factor (ANF), pro-alpha1(III) collagen, and transforming growth factor beta1 (TGF-beta1)
genes. We tested the hypotheses that angiotensin-converting enzyme inhibition (ACEI) in SHR would prevent and reverse HF-associated changes
in gene expression when administered prior to and after the onset of HF,
respectively. We also investigated the effect of ACEI on circulating and cardiac components of the renin-angiotensin system. ACEI (captopril 2 g/L
in the drinking water) was initiated at 12, 18, and 21 months of age in SHR without HF and in SHR with HF. Results were compared with those of
age-matched normortensive Wistar-Kyoto (WKY) rats, and to untreated SHR
with and without evidence of HF. ACEI initiated prior to failure prevented the changes in **alpha-MHC**, ANF, pro-alpha1,(III)
collagen, and TGF-beta1 gene expression that are associated with the transition to HF. ACEI initiated after the onset of HF lowered levels of TGF-beta1 mRNA by 50% (P<.05) and elevated levels of **alpha-MHC** mRNA two- to threefold (P<.05). Circulating levels of renin and angiotensin I were elevated four- to sixfold by ACEI, but surprisingly, plasma levels of angiotensin II were not reduced. ACEI increased LV renin mRNA levels in WKY and SHR by two- to threefold but did
not influence LV levels of angiotensinogen mRNA. The results suggest that
the anti-HF benefits of ACEI in SHR may be mediated, at least in part, by
effects on the expression of specific genes, including those encoding **alpha-MHC**, ANF, TGF-beta1, pro-alpha1(III) collagen, and renin-angiotensin system components.

L7 ANSWER 9 OF 14 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 4
ACCESSION NUMBER: 97368208 EMBASE
DOCUMENT NUMBER: 1997368208
TITLE: Embryonic gene expression in nonoverloaded ventricles of hereditary hypertrophic cardiomyopathic hamsters.
AUTHOR: Di Nardo P.; Fiaccavento R.; Natali A.; Minieri M.; Sampaolesi M.; Fusco A.; Janmot C.; Cuda G.; Carbone A.; Rogliani P.; Peruzzi G.
CORPORATE SOURCE: Dr. P. Di Nardo, Lab. di Cardiol. Molec./Cellulare, Dipartmento di Medicina Interna, Universita di Roma 'Tor Vergata', 00173 Roma, Italy
SOURCE: Laboratory Investigation, (1997) 77/5 (489-502).
Refs: 34
ISSN: 0023-6837 CODEN: LAINAW
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
018 Cardiovascular Diseases and Cardiovascular Surgery
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Current information regarding the molecular and biochemical mechanisms of
myocardial hypertrophy, as obtained from isolated cardiomyocytes and/or healthy animals with aortic banding, does not permit
dissection of the hierarchical relationship among different steps and triggers of the pathogenic process in vivo. The aim of the present study was to depict the temporal relationship among myocardial structural and

functional characteristics, the embryonic gene program, and transforming growth factor (TGF).beta.1 expression in euthyroid hereditary hypertrophic cardiomyopathic hamsters (CMPH). This investigation was performed using Western and Northern blot and in situ hybridization techniques. The results show that in CMPH, the severity of the hemodynamic overload is not related to any modification in structural myocardial characteristics (cardiac mass, cardiomyocyte dimensions, total RNA, and protein content), whereas an early activation of the embryonic gene program occurs in not yet overloaded 90-day-old CMPH (left ventricular end diastolic pressure < 15 mm Hg). In these animals, a 30% to 90% decrease in the .**alpha** . **myosin heavy chain** (.**alpha**. **MHC**) relative content was found in ventricles, whereas .beta.MHC increased 5-fold. In addition, the .alpha. skeletal actin expression was enhanced 2-fold versus age-matched controls. No modifications were observed in myosin function evaluated by in vitro tactility assay, whereas the administration of L-thyroxine (100 .mu.g/kg intraperitoneally daily) to CMPH was able to reinduce the ventricular expression of the . **alpha.MHC** isoform (5-fold increase). Conversely, no changes were found in .alpha. cardiac actin and myosin light chain 2 (MLC2) expression. A close temporal relationship occurred in CMPH ventricles between the re- expression of the embryonic gene program and a 3-fold enhancement of the expression of TGF.beta.1. These results indicate that the CMPH provides a useful model for investigating the expression of embryonic genes in hypertrophic ventricles in the absence of mechanical and hormonal stimuli, and that TGF.beta.1 is involved in regulating in vivo the 'embryonic step' of **myocardial hypertrophy**. Furthermore, the study offers new insights into the pathophysiologic mechanisms leading to heart failure.

L7 ANSWER 10 OF 14 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1997:479508 BIOSIS
DOCUMENT NUMBER: PREV199799778711
TITLE: Gender specific regulation of gene expression in the hypertrophied myocardium by oestrogens.
AUTHOR(S): Pelzer, Theo; Shamim, Asiya; Woelfges, Simone; Schumann, Michael; Neyses, Ludwig
CORPORATE SOURCE: Dep. Med., Univ. Wuerzburg, Wuerzburg Germany
SOURCE: European Heart Journal, (1997) Vol. 18, No. ABSTR. SUPPL., pp. 231.
Meeting Info.: XIXth Congress of the European Society of Cardiology together with the 32nd Annual General Meeting of the Association of European Paediatric Cardiologists (AEPC) Stockholm, Sweden August 24-28, 1997
ISSN: 0195-668X.
DOCUMENT TYPE: Conference; Abstract; Conference
LANGUAGE: English

L7 ANSWER 11 OF 14 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1997:374550 BIOSIS
DOCUMENT NUMBER: PREV199799673753
TITLE: Cardiac G-alpha-q overexpression causes spontaneous **myocardial hypertrophy** with failure in pregnancy.
AUTHOR(S): Sakata, Yoshihito; D'Angelo, Drew D.; Dorn, Gerlad W. li
CORPORATE SOURCE: Univ. Cincinnati, Cincinnati, OH USA
SOURCE: Journal of Molecular and Cellular Cardiology, (1997) Vol. 29, No. 6, pp. A157.
Meeting Info.: XIX Annual Meeting of the International Society for Heart Research (American Section) on Cardiovascular Injury, Repair and Adaptation Vancouver, British Columbia July 23-27, 1997
ISSN: 0022-2828.
DOCUMENT TYPE: Conference; Abstract
LANGUAGE: English

L7 ANSWER 12 OF 14 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 5
ACCESSION NUMBER: 93116141 EMBASE
DOCUMENT NUMBER: 1993116141
TITLE: Correlated expression of atrial myosin heavy chain and regulatory light chain isoforms with pressure overload hypertrophy in the non-human primate.
AUTHOR: Henkel R.D.; Kammerer C.M.; Escobedo L.V.; VandeBerg J.L.; Walsh R.A.
CORPORATE SOURCE: Department of Medicine, Division of Cardiology, University of Cincinnati, 231 Bethesda Avenue,Cincinnati, OH 45267-0542, United States
SOURCE: Cardiovascular Research, (1993) 27/3 (416-422). ISSN: 0008-6363 CODEN: CVREAU
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Objective: The aim was to determine the extent to which myosin heavy chain and light chain isoform transitions in atrial myocardium are coordinately regulated under pathological conditions in tissue from normal baboons, hypertensive baboons with **myocardial hypertrophy**, and baboons in which hypertrophy had regressed. Methods: Quantitative distributions of myosin heavy chain (MHC) and regulatory myosin light chain (MLC2) isoforms in atrial myocardium from 35 adult baboons were determined by electrophoresis under denaturing conditions and laser densitometry. Results: A significant association was observed between the ratios of MHC and MLC2 isoforms in atrial myocardium (r=0.73, p<0.001, n=69). Expressions of .**alpha**. **MHC** and atrial MLC2 (ALC2) isoforms were correlated in atrial myocardium, as were those of .beta. MHC and ventricular MLC2 (VLC2) isoforms. In a subset of baboons with experimentally induced renal hypertension (n=12) both .beta. MHC and VLC2 isoforms were found at higher levels in left atria than were present in normotensive baboons (p=0.006, n=15). Left atria from hypertensive baboons with regressed LVH contained intermediate levels of both .beta. MHC and VLC2 isoforms. Conclusions: There is tight coupling between the expression of myosin subunit isoforms under pathological conditions from a primate species closely related to humans. The data suggest that the synthesis of these subunits of myosin may be coordinated at the molecular level.

L7 ANSWER 13 OF 14 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1990:482372 BIOSIS
DOCUMENT NUMBER: BR39:106393
TITLE: MYOCARDIAL CELLS EARLY CHANGES IN THE EXPRESSION AND DISTRIBUTION OF PROTEINS OR THEIR MESSENGER RNA DURING THE DEVELOPMENT OF **MYOCARDIAL HYPERTROPHY** IN THE RAT.
AUTHOR(S): SAMUEL J-L; SCHIAFFINO S; RAPPAPORT L
CORPORATE SOURCE: INSERM U127, HOPITAL LARIBOISIERE, 41 BLVD. DE LA CHAPELLE, 75010 PARIS, FR.
SOURCE: SWYNGHEDAUW, B. (ED.). RESEARCH IN: CARDIAC HYPERTROPHY AND FAILURE. XVI+696P. LES EDITIONS INSERM: PARIS, FRANCE; JOHN LIBBEY EUROTEXT LTD.: LONDON, ENGLAND, UK. ILLUS, (1990) 0 (0), 277-292.
ISBN: 2-85598-423-8, 0-86196-234-6.
FILE SEGMENT: BR; OLD
LANGUAGE: English

L7 ANSWER 14 OF 14 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1987:398030 BIOSIS
DOCUMENT NUMBER: BA84:74210
TITLE: MYOSIN ISOZYME SYNTHESIS AND MESSENGER RNA LEVELS IN PRESSURE-OVERLOADED RABBIT HEARTS.
AUTHOR(S): NAGAI R; PRITZL N; LOW R B; STIREWALT W S; ZAK R; ALPERT N R; LITTEN R Z
CORPORATE SOURCE: DEP. PHYSIOL. BIOPHYSICS, COLL. MED., UNIV. VERMONT, BURLINGTON, VT. 05405.
SOURCE: CIRC RES, (1987) 60 (5), 692-699. CODEN: CIRUAL. ISSN: 0009-7330.
FILE SEGMENT: BA; OLD

LANGUAGE: English
AB The in vivo synthesis rats of myosin isozyme heavy chains .beta. and .alpha. were measured in right ventricular (RV) muscle at 2 and 4 days following pulmonary artery constriction in rabbits, together with measurements of their relative mRNA levels. The synthesis rate of .beta.-myosin heavy chains was elevated in 2-day (0.27 .+-. 0.06 day-1 or 2.5 .+-. 0.7 mg/g RV/day, mean .+-. SD) and in 4-day (0.25 .+-. 0.08 day-1 or 2.8 .+-. 1.0 mg/g RV/day) pressure overload, when compared to untreated rabbits (0.15 .+-. 0.04 day-1 or 1.5 .+-. 0.4 mg/g RV/day). However, the synthesis rates of **.alpha.-myosin heavy chains** in the same hearts were not altered significantly. There was a differential increase in the fractional synthesis rate of .beta. vs. .alpha. heavy chains 2-day and 4-day pressure overload and in 2-day shams, suggesting switching toward .beta. heavy chain synthesis had occurred at these time points. .beta. heavy chain synthesis, as a proportion of total (.alpha. + .beta.) heavy chain synthesis, was significantly higher in 4-day pressure overload (78 .+-. 9%) than in 4-day sham rabbit (63 .+-. 6%). This increase in relative .beta.-synthesis was associated with a significant increase in the relative proportion of .beta. heavy chain mRNA level (76 .+-. 13% vs. 56 .+-. 7%). Furthermore, relative .beta.-synthesis and the .beta.-mRNA levels correlated linearly with each other in all experimental groups. We concluded that the during the early stages of pressure overload 1) the synthesis rate of .beta.-myosin heavy chain is accelerated without a reciprocal decrease in a **.alpha.-myosin heavy chain** synthesis, and 2) an increase in .beta.-myosin heavy chain expression appears to be achieved mainly by modulation of pretranslational events.

=> d his

(FILE 'HOME' ENTERED AT 16:51:34 ON 30 APR 2001)

FILE 'EMBASE, BIOSIS, MEDLINE, CAPLUS, LIFESCI' ENTERED AT 16:51:48 ON 30 APR 2001
L1 1956 S ((MYOCARDIAL FAILURE) OR (MYOCARDIAL HYPERTROPHY)(50A)(TREATM
L2 1766 S ((ALPHA MYOSIN HEAVY CHAIN) OR (ALPHA-MHC))
L3 11 S L1 AND L2
L4 5 DUP REM L3 (6 DUPLICATES REMOVED)
L5 6243 S (MYOCARDIAL FAILURE) OR (MYOCARDIAL HYPERTROPHY)
L6 29 S L2 AND L5
L7 14 DUP REM L6 (15 DUPLICATES REMOVED)

=> s l5 and (gene therapy) and l2
L8 1 L5 AND (GENE THERAPY) AND L2

=> d l8 ibib abs

L8 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:96374 CAPLUS
DOCUMENT NUMBER: 130:152121
TITLE: Intracellular inhibitors of Gq protein signaling and their role in the control of **myocardial hypertrophy**
INVENTOR(S): Koch, Walter J.; Lefkowitz, Robert J.; Akhter, Shahab A.; Luttrell, Louis M.
PATENT ASSIGNEE(S): Duke University, USA
SOURCE: PCT Int. Appl., 44 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9905294	A1	19990204	WO 1998-US15152	19980724
W: AU, CA, JP				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9885793	A1	19990216	AU 1998-85793	19980724
EP 1012313	A1	20000628	EP 1998-936973	19980724
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				

PRIORITY APPLN. INFO.: US 1997-53659 P 19970724
WO 1998-US15152 W 19980724
AB Methods of preventing or limiting **myocardial hypertrophy** by inhibiting Gq-coupled receptor signaling in myocardial tissue are described. In particular, a C-terminal peptide of the .alpha. subunit of Gq is shown to inhibit Gq signalling and to block hypertrophy-assocd. events in animal cell culture and in transgenic animals. Transgenic mice expressing a gene for the C-terminal peptide (305-359) of the Gq .alpha. subunit using the myocardium-specific **.alpha.-myosin heavy chain** gene were prepd. by std. methods. In these mice, the p24/p44 MAP kinase activity in the myocardium was induced 1.3-fold by angiotensin II and endothelin I. In control mice, kinase induction was .apprx.4-fold. The effect was specific for Gq-coupled receptors as the peptide did not affect basal or .beta.2-adrenoceptor-mediated increases in adenyl cyclase activity. The transgenic mice were also resistant to pressure overload hypertrophy brought on by surgical transverse aortic constriction.
REFERENCE COUNT: 6
REFERENCE(S): (1) Akhter; Science 1998, V280, P574 CAPLUS
(2) D'Angelo; Proc Natl Acad Sci USA 1997, V94, P8121 CAPLUS
(3) Lamorte; J Biol Chem 1994, V269(18), P13490 CAPLUS
(4) Meij, J; Molec and Cellular Biochem 1996, V157, P31 CAPLUS
(5) Sah; J Biol Chem 1996, V271(49), P31185 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d his

(FILE 'HOME' ENTERED AT 16:51:34 ON 30 APR 2001)

FILE 'EMBASE, BIOSIS, MEDLINE, CAPLUS, LIFESCI' ENTERED AT 16:51:48 ON 30 APR 2001
L1 1956 S ((MYOCARDIAL FAILURE) OR (MYOCARDIAL HYPERTROPHY)(50A)(TREATM
L2 1766 S ((ALPHA MYOSIN HEAVY CHAIN) OR (ALPHA-MHC))
L3 11 S L1 AND L2
L4 5 DUP REM L3 (6 DUPLICATES REMOVED)
L5 6243 S (MYOCARDIAL FAILURE) OR (MYOCARDIAL HYPERTROPHY)
L6 29 S L2 AND L5
L7 14 DUP REM L6 (15 DUPLICATES REMOVED)
L8 1 S L5 AND (GENE THERAPY) AND L2

=> s l2 and (gene therapy)
L9 17 L2 AND (GENE THERAPY)

=> dup rem l9
PROCESSING COMPLETED FOR L9
L10 11 DUP REM L9 (6 DUPLICATES REMOVED)

=> d l10 1-11 ibib abs

L10 ANSWER 1 OF 11 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:100672 CAPLUS
DOCUMENT NUMBER: 132:249395
TITLE: RXR.alpha. overexpression in cardiomyocytes causes dilated cardiomyopathy but fails to rescue myocardial hypoplasia in RXR.alpha.-null fetuses
AUTHOR(S): Subbarayan, Vemparala; Mark, Manuel; Messadeq, Nadia; Rustin, Pierre; Chambon, Pierre; Kastner, Philippe
CORPORATE SOURCE: Institut de Genetique er de Biologie Moleculaire et Cellulaire, CNRS-INSERM-ULP-College de France, Illkirch, 67404, Fr.
SOURCE: J. Clin. Invest. (2000), 105(3), 387-394
CODEN: JCINAO; ISSN: 0021-9738
PUBLISHER: American Society for Clinical Investigation
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Retinoid X receptor .alpha.-null (RXR.alpha.-null) mutants exhibit hypoplasia of their ventricular myocardium and die at the fetal stage. In the present study, the authors wished to det. whether transgenic re-expression of RXR.alpha. in mutant cardiac myocytes could rescue these defects. Two transgenic mouse lines specifically overexpressing an RXR.alpha. protein in cardiomyocytes were generated, using the cardiac . **alpha.-myosin heavy chain** (. **alpha.-MHC**) promoter. Breeding the high copy no. transgenic line onto an RXR.alpha.-null genetic background did not

prevent
the myocardial hypoplasia and fetal lethality assocd. with the RXR.alpha.-/- genotype, even though the transgene was expressed in the
ventricles as early as 10.5 days post-coitum. These data suggest that the
RXR.alpha. function involved in myocardial growth may correspond to a non-cell-autonomous requirement for a signal orchestrating the growth and
differentiation of myocytes. Interestingly, the adult transgenic mice developed a dilated cardiomyopathy, assocd. with myofibrillar abnormalities and specific deficiencies in respiratory chain complexes I and II, thus providing an addnl. model for this genetically complex disease.
REFERENCE COUNT: 39
REFERENCE(S): (1) Andrews, N; Nucleic Acids Res 1991, V19, P2499
CAPLUS
(2) Antozzi, C; Cardiovasc Res 1997, V35, P184 CAPLUS
(3) Brocard, J; Biochem Biophys Res Commun 1996, V229, P211 CAPLUS
(4) Chambon, P; FASEB J 1996, V10, P940 CAPLUS
(5) Chen, J; Development 1998, V125, P1943 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 2 OF 11 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:784130 CAPLUS
DOCUMENT NUMBER: 132:9638
TITLE: adenoviral **gene therapy** methods for altering cardiac cell disease phenotype
INVENTOR(S): Engler, Robert L.
PATENT ASSIGNEE(S): Collateral Therapeutics, USA
SOURCE: PCT Int. Appl., 87 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9962940	A2	19991209	WO 1999-US11961	19990528
WO 9962940	A3	20000615		

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
AU 9943212 A1 19991220 AU 1999-43212 19990528
EP 1085910 A2 20010328 EP 1999-955272 19990528
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI
PRIORITY APPLN. INFO.: US 1998-87380 P 19980530
WO 1999-US11961 W 19990528

AB Methods for improving or maintaining cardiac function in patients are disclosed. The methods include the stimulation of heart muscle regeneration, the treatment of patients with congestive heart failure and the prevention of organ transplant rejection. Methods are also disclosed for the treatment of patients after myocardial infarction and/or patients with congestive heart failure by adenovirus-mediated delivery of peptides, including, but not limited to, NKX-2.5, MEF2, GATA4, BCL-2, HGH, and Fas ligand, that alter the phenotype of cells in the heart. These have the potential to induce cardiomyocyte differentiation. Treatment of congestive heart failure with BCL-2 therapy prevents apoptosis. This adenoviral vector has the E1A and E1B genes deleted. A dog myocardial infarction model is described. A pig model of congestive heart failure is provided. With this therapy, a delay of atherosclerosis is also achieved as well as prevention of heart cell loss. Other therapeutic proteins include the chimeric protein of the HGH transgene fused at its 5'-end to a proteoglycan binding domain of VEGF145. Myofibroblasts and myocytes are targeted with these vectors and delivered by coronary sinus retroprofusion or intracoronary injection into coronary artery or blood vessel, or saphenous vein graft or internal mammary artery graft lumen region. An inflatable balloon catheter coated with vector is also employed to deliver the transgene. Heart cell-specific promoters such as ventricular myosin light chain-2 or **alpha myosin heavy chain** or fibroblast-specific or myofibroblast-specific promoters are provided.

L10 ANSWER 3 OF 11 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:96374 CAPLUS
DOCUMENT NUMBER: 130:152121
TITLE: Intracellular inhibitors of Gq protein signaling and their role in the control of myocardial hypertrophy
INVENTOR(S): Koch, Walter J.; Lefkowitz, Robert J.; Akhter, Shahab A.; Luttrell, Louis M.
PATENT ASSIGNEE(S): Duke University, USA
SOURCE: PCT Int. Appl., 44 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9905294	A1	19990204	WO 1998-US15152	19980724

W: AU, CA, JP
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE
AU 9885793 A1 19990216 AU 1998-85793 19980724
EP 1012313 A1 20000628 EP 1998-936973 19980724
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI
PRIORITY APPLN. INFO.: US 1997-53659 P 19970724
WO 1998-US15152 W 19980724

AB Methods of preventing or limiting myocardial hypertrophy by inhibiting Gq-coupled receptor signaling in myocardial tissue are described. In particular, a C-terminal peptide of the .alpha. subunit of Gq is shown to inhibit Gq signaling and to block hypertrophy-assocd. events in animal cell culture and in transgenic animals. Transgenic mice expressing a gene for the C-terminal peptide (305-359) of the Gq .alpha. subunit using the myocardium-specific .**alpha.-myosin heavy chain** gene were prepd. by std. methods. In these mice, the p24/p44 MAP kinase activity in the myocardium was induced 1.3-fold by angiotensin II and endothelin I. In control mice, kinase induction was .apprx.4-fold. The effect was specific for Gq-coupled receptors as the peptide did not affect basal or .beta.2-adrenoceptor-mediated increases in adenyl cyclase activity. The transgenic mice were also resistant to pressure overload hypertrophy brought on by surgical transverse aortic constriction.
REFERENCE COUNT: 6
REFERENCE(S): (1) Akhter; Science 1998, V280, P574 CAPLUS
(2) D'Angelo; Proc Natl Acad Sci USA 1997, V94, P8121 CAPLUS
(3) Lamorte; J Biol Chem 1994, V269(18), P13490 CAPLUS
(4) Meij, J; Molec and Cellular Biochem 1996, V157, P31 CAPLUS
(5) Sah; J Biol Chem 1996, V271(49), P31185 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 4 OF 11 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:45078 CAPLUS
DOCUMENT NUMBER: 130:106033
TITLE: Antisense DNA constructs for expression of hybrid mRNAs driven by inducible tissue-specific promoters
INVENTOR(S): Malbon, Craig C.; Moxham, Christopher M.
PATENT ASSIGNEE(S): The Research Foundation of State University of New York, USA
SOURCE: U.S., 19 pp., Cont.-in-part of U.S. Ser. No. 241,796, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5858774	A	19990112	US 1995-543559	19951016
US 6133245	A	20001017	US 1998-96833	19980612

PRIORITY APPLN. INFO.: US 1994-241796 B2 19940512
US 1995-543559 A1 19951016
AB A gene is regulated by introducing into a cell an inducible, tissue-specific antisense DNA construct. The antisense DNA construct comprises any inducible, tissue-specific gene, into which a DNA sequence antisense to any DNA sequence of the gene targeted for regulation has been inserted. The inducible, tissue-specific antisense DNA construct transcribes a hybrid mRNA contg. an RNA sequence antisense to a sequence of the mRNA of the gene targeted for regulation. The hybrid mRNA also contains the RNA sequence of the inducible, tissue-specific gene. Some examples of suitable inducible genes include those selected from the group consisting of mammalian cytosolic phosphoenolpyruvate carboxykinase (PEPCK) (GTP, EC 4.1.1.32), mammalian atrial natriuretic factor (ANF), and mammalian .**alpha. myosin heavy chain** (.**alpha.-MHC**). In a preferred embodiment, the inducible, tissue-specific gene is the rat PEPCK gene. Thus a DNA sequence having 39 bases that transcribe an RNA antisense to 39 bases to Gi .alpha.2-subunit is used to inhibit expression of this important G protein gene. The pLNCX vector, which contains an ampicillin gene and neomycin resistance and retroviral packaging genes under the control of the mouse Moloney virus long terminal repeats is used, with the antisense sequences under the control of the cytomegalovirus. Each of the founder mice and their transgenic offspring displayed sharply reduced G.alpha.i2 expression in tissues in which the PEPCK gene is expressed, i.e., in fat, liver and in some cases kidney.
REFERENCE COUNT: 27
REFERENCE(S): (1) Anon; WO 9116426 1991 CAPLUS
(2) Bird; US 5254800 1993 CAPLUS
(4) Coleman; Cell 1984, V37, P429 CAPLUS
(5) Crowley; Cell 1985, V43, P633 CAPLUS
(6) Eppstein; US 4946787 1990 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 5 OF 11 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:393034 CAPLUS
DOCUMENT NUMBER: 131:40554
TITLE: Oncogene or virus induced multistep expression systems for **gene therapy**
INVENTOR(S): Muller, Rolf; Sedlacek, Hans-Harald
PATENT ASSIGNEE(S): Hoechst Marion Roussel Deutschland GmbH, Germany
SOURCE: Eur. Pat. Appl., 44 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 922768	A2	19990616	EP 1998-121471	19981111
EP 922768	A3	20000105		

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO

DE 19751587	A1	19990729	DE 1997-19751587	19971121
AU 9893256	A1	19990610	AU 1998-93256	19981119
CN 1221033	A	19990630	CN 1998-122537	19981120
BR 9804720	A	20000328	BR 1998-4720	19981120
JP 2000106886	A2	20000418	JP 1998-333200	19981124

PRIORITY APPLN. INFO.: DE 1997-19751587 A 19971121
AB The invention concerns a DNA construct for the expression of an effector gene contg. promoter I (component a) that regulates the expression of the transcription factor gene (component b); promoter II (component c) that is specifically bound by the product of he transcription factor gene and that regulates the expression of the effector gene (component d); all components are part of the same DNA construct; the activity of the gene product of the transcription factor gene is dependent on one or more cellular regulatory protein(s), that bind specifically to the gene product and influence its activity. The invention also concerns cells hosting the construct and the application for **gene therapy** and prodn. of gene therapeutics. Effector genes are coding for pharmacol. active substances, pharmacons, enzymes or their precursors, or fusion proteins with signal proteins; and are used for therapy or prophylaxis. In one of the versions the component b consists of the b1 activation domain, the b2 regulatory protein binding sequence, and the b3 DNA-binding domain for a transcription factor. The b2 sequence is a viral or bacterial binding protein sequence; this ensures that in healthy cells the function of the transcription factor gene is inhibited; regulatory proteins that are produced in infected cells bind to the sequence; thus the transcription factor becomes activated. In a specific version b2 represents an antibody or antibody fragment with VH or VL binding sequences for a regulatory protein; humanized murine antibodies, recombinant antibody fragments produced in hybridoma cells, or isolates from libraries are used. DNA expressing the antibody fragments are ligated to b1 and b3 components. Examples of activation domains (component b1) are: cDNA for the acidic transactivation domain of HSV1-VP16, activation domain of Oct-2, SP1, NFY etc. Examples of DNA-binding domains (component b2) are: cDNA for the DNA-binding domains of Gal4 protein, LEXA protein, lac-repressor protein, etc. In another version the construct consist of promoter I (component a'), the repressor (component b'); the activation sequence (component c1) induced by b'; the DNA binding sequence for the repressor protein (component c2). The promoter I (component a') consists of a DNA-binding sequence for a regulatory protein (component a1), and a basal promoter (component a2).
Examples for component a1 are: the DNA binding sequences of p53 protein, Wt-1 protein, NF-Kappa B protein, E2f/DP1 complex, and Myc/Max protein.
Examples for component a2 are: the basal promoter of SV40, c-fos, U2 sn RNA-promoter, HSV TK promoter. Activation sequences are (component a or component c1): non-constitutive activation promoters, e.g. promoters of RNA polymerase II and III, CMV promoter and enhancer, SV40 promoter; viral promoters and activation sequences, e.g. HBV, HCV, HIV, etc.; promoters with metabolic activation, e.g. hypoxia induced enhancer; promoters that are activated cell cycle-specific, e.g. promoters of the genes cdc25c, Cyolin A etc.; tetracyclin induced promoters; cell specific promoters, e.g. promoters and activation sequences of endothelial cells, or of contiguous cells, smooth muscle cells, glial cells etc. The effector genes are for tumor therapy, with the following target cells: endothelium, stroma cells, muscle cells, tumor cells, leukemia cells. The effector genes include cell specific promoters, inhibitors for cell proliferation, blood activation factor inducing genes, angiogenesis inhibitors, cytostatics, cytotoxics, cytokines, growth factors, etc. also in form of fusion proteins.

L10 ANSWER 6 OF 11 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:260866 CAPLUS
DOCUMENT NUMBER: 133:217500
TITLE: Tissue-specific gene delivery by recombinant adenoviruses containing cardiac-specific promoters
AUTHOR(S): Franz, Wolfgang-Michael; Rothmann, Thomas; Muller, Matthias; Frey, Norbert; Katus, Hugo Albert
CORPORATE SOURCE: Neth.
SOURCE: Dev. Cardiovasc. Med. (1999), 214(Cardiovascular Specific Gene Expression), 301-317
CODEN: DCMEDM; ISSN: 0166-9842
PUBLISHER: Kluwer Academic Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Expts. demonstrated that the ventricular specific myosin-light-chain 2 promoter retains its in vivo specificity of gene expression in the myocardium after incorporation into an adenoviral vector, Ad-MLCLuc. Specific gene expression of AdMLCLuc was shown in the ventricular myocardium after injection into the cardiac cavity of newborn rats. In contrast, when the adenoviral vector AdMHCLuc, in which the .**alpha** .-**myosin heavy chain** promoter was used to drive luciferase, was used, the reporter gene was active in ventricular and atrial myocardium, and revealed ectopic expression in lung as well as in liver tissue. For **gene therapy** of cardiovascular diseases, it is useful to target recombinant gene expression to the myocardium. Previous attempts of adenoviral gene transfer have not allowed a restricted gene expression in cardiac cells. The finding that administration of recombinant adenovirus resulted in infection and expression of the transgene in many non-cardiac tissues raises important safety concerns. Such undesired effects could be avoided by using the adenoviral vector Ad-MLCLuc, which allows a ventricular muscle-specific gene expression.

REFERENCE COUNT: 41
REFERENCE(S): (1) Acsadi, G; Hum Mol Gen 1994, V3, P579 CAPLUS
(3) Barr, E; Gene Ther 1994, V1, P51 CAPLUS
(4) Bett, A; Proc Natl Acad Sci USA 1994, V91, P8802 CAPLUS
(6) de Wet, J; Mol Cell Biol 1987, V7, P725 CAPLUS
(9) Engelhardt, J; Proc Natl Acad Sci USA 1994, V91, P6196 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 7 OF 11 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:684944 CAPLUS
DOCUMENT NUMBER: 129:271507
TITLE: Human .beta.1-adrenergic receptor gene and heart tissue-specific **.alpha.-myosin heavy chain** gene promoter in transgenic mouse model and treatment for heart disease
INVENTOR(S): Port, J. David; Bristow, Michael R.
PATENT ASSIGNEE(S): University Technology Corp., USA
SOURCE: PCT Int. Appl., 41 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9844092	A1	19981008	WO 1998-US6791	19980402
US 6218597	B1	20010417	US 1998-53293	19980401
AU 9868863	A1	19981022	AU 1998-68863	19980402

PRIORITY APPLN. INFO.: US 1997-41966 P 19970403
WO 1998-US6791 W 19980402

AB The invention provides a transgenic mouse that is a model for heart muscle disease and heart failure. Also provided are methods of using the transgenic mouse model to study heart muscle disease and heart failure and conditions and treatments related thereto. The invention also provides a method of **gene therapy** for the treatment of human heart failure. The transgenic mouse contains a transgene comprising a heart tissue-specific promoter from the **.alpha.-myosin heavy-chain** gene operatively linked to the gene for the human .beta.1-adrenergic receptor. In the transgenic mouse model, the .beta.1-adrenergic receptor gene is overexpressed .gtoreq.40-fold over the level of expression in transgene-neg. animals.

L10 ANSWER 8 OF 11 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:174649 CAPLUS
DOCUMENT NUMBER: 128:317735
TITLE: Efficient transfer of genes into murine cardiac grafts by starburst polyamidoamine dendrimers
AUTHOR(S): Qin, Lihui; Pahud, Dominique R.; Ding, Yaozhong; Bielinska, Anna U.; Kukowska-Latallo, Jolanta F.; Baker, James R., Jr.; Bromberg, Jonathan S.
CORPORATE SOURCE: Departments of Surgery and Microbiology and Immunology, University of Michigan, Ann Arbor, MI, 48109, USA
SOURCE: Hum. Gene Ther. (1998), 9(4), 553-560
CODEN: HGTHE3; ISSN: 1043-0342
PUBLISHER: Mary Ann Liebert, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Starburst dendrimer, a structurally defined, spherical macromol. composed of repeating polyamidoamino subunits, was investigated to augment plasmid-mediated gene transfer efficiency in a murine cardiac transplantation model. The grafts were directly injected with naked pCH110, a plasmid encoding .beta.-galactosidase (.beta.-Gal), or pCH110-dendrimer complex, and reporter gene expression detd. by X-Gal staining. The grafts injected with pCH110-dendrimer demonstrated widespread and extended .beta.-Gal expression in both myocytes and the graft infiltrating cells from 7 to 28 days, compared to the grafts injected with naked pCH110 that expressed .beta.-Gal only in myocytes for less than 14 days. Plasmid p.**alpha.MHC**-vIL-10, encoding viral interleukin-10 (vIL-10) under the control of **.alpha.-myosin heavy chain** promoter, was able to prolong allograft survival from 13.9 .+-. 0.9 days to 21.4 .+-. 2.3 days ($p < 0.005$). When dendrimer G5EDA was used with p.**alpha.MHC**-vIL-10, 60-fold less DNA resulted in significant prolongation of graft survival to 38.6 .+-. 4.7 days ($p < 0.0005$). The dose of DNA, the charge ratio of DNA to dendrimer, and the size generation of the dendrimers were all detd. to be crit. variables for prolongation of allograft survival in this model system. Thus, the use of the starburst dendrimer dramatically increased the efficiency of plasmid-mediated gene transfer and expression. Prodn. of immunosuppressive cytokines at higher amts. for longer periods of time in a greater expanse of tissue enhanced the immunosuppressive effect and prolonged graft survival further.

L10 ANSWER 9 OF 11 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 1
ACCESSION NUMBER: 97338245 EMBASE
DOCUMENT NUMBER: 1997338245
TITLE: Regulated expression of a foreign gene targeted to the ischaemic myocardium.
AUTHOR: Prentice H.; Bishopric N.H.; Hicks M.N.; Discher D.J.; Wu X.; Wylie A.A.; Webster K.A.
CORPORATE SOURCE: K.A. Webster, Dept. of Molecular/Cell. Pharmacol., Rosenstiel Medical Science Building, University of Miami, 1600 NW Tenth Avenue, Menlo Park, CA, United States. kwebster@chroma.med.miami.edu
SOURCE: Cardiovascular Research, (1997) 35/3 (567-574).
Refs: 64
ISSN: 0008-6363 CODEN: CVREAU
PUBLISHER IDENT.: S 0008-6363(97)00158-2
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Objectives: Regulated expression of transferred foreign genes may be an important feature of **gene therapy**. Because coronary artery disease often involves intermittent myocardial ischaemia followed by periods of normal cardiac function it will probably be necessary to regulate the expression of putative therapeutic/cardioprotective genes directly in response to ischaemia-associated signals. The objectives of the current study were to develop a combination of gene regulatory components that can be used to target a product to the myocardium and limit the expression of the gene to periods of ischaemic activity. Methods: Expression plasmids were constructed containing muscle-specific promoters and hypoxia-responsive enhancer elements linked to a reporter gene. The regulation of these constructs by hypoxia or experimental ischaemia was measured following transient expression in cultured cells or after direct injection of DNA into the rabbit myocardium. Results: A single set of hypoxia response elements placed immediately upstream of the minimal muscle-specific **.alpha.-myosin heavy chain** promoter conferred potent positive regulation of this promoter by hypoxia in vitro and by ischaemia in vivo. Induction by ischaemia persisted for at least 4 h and returned to the baseline level within 8 h. Conclusions: Hypoxia responsive regulatory elements, in combination with weak tissue-restricted promoters incorporated into an appropriate vector system may allow controlled expression of a therapeutic gene in ischaemic myocardium.

L10 ANSWER 10 OF 11 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 2
ACCESSION NUMBER: 97338244 EMBASE
DOCUMENT NUMBER: 1997338244
TITLE: Analysis of tissue-specific gene delivery by recombinant adenoviruses containing cardiac-specific promoters.
AUTHOR: Franz W.-M.; Rothmann T.; Frey N.; Katus H.A.
CORPORATE SOURCE: W.-M. Franz, Medizinische Klinik 11, Medizinische Universitat zu Lubeck, Ratzeburger, Allee 160, 23538 Lubeck, Germany. franz@medinf.mu-luebeck.de
SOURCE: Cardiovascular Research, (1997) 35/3 (560-566).

Refs: 32
ISSN: 0008-6363 CODEN: CVREAU
PUBLISHER IDENT.: S 0008-6363(97)00154-5
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Objective: To approach heart muscle diseases by gene transfer, an adenoviral vector system was intended to be established suitable for gene expression in ventricular and/or atrial myocardium. Methods: Two adenoviral vectors (Ad-mhcLuc; Ad-mlcLuc) were constructed, in which the luciferase reporter gene is under control of either the ventricle-specific myosin light chain-2 (mlc-2v) or the atrial- and ventricular-specific . **alpha.-myosin heavy chain** (. **alpha.-mhc**) promoter. For controls, a recombinant adenovirus without promoter (Ad-Luc) and one with the Rous sarcoma virus (rsv) promoter (Ad- rsvLuc) were generated. A volume of 20 .mu.l containing 2 x 109 plaque forming units (pfu) of the recombinant adenoviruses Ad-mhcLuc, Ad-mlcLuc, Ad-rsvLuc or Ad-Luc was injected into the cardiac cavity or the quadriceps femoris muscle of neonatal rats. After five days animals were sacrificed and nine different tissues were analyzed for reporter gene expression by detection of light activity relative to mg of tissue. Results: Injections of recombinant adenoviruses into the cardiac cavity of neonatal rats resulted in heart- specific gene expression of Ad-mlcLuc (20 fold of Ad-Luc; 11% of Ad-rsvLuc), whereas Adz-mhcLuc gave mainly luciferase activity in the heart (6.5 fold of Ad-Luc; 3% of Ad-rsvLuc) with additional activity in lung and liver (2-4 fold of Ad-Luc). In the ventricular tissue Ad-mlcLuc revealed a 35-fold higher luciferase activity, whereas Adr-mhcLuc, Ad-rsvLuc and Ad-Luc showed only 2- fold higher luciferase activities compared to the atrium. Viral DNA in atrial and ventricular tissue was detected by PCR at approximately the same abundance independent of the injected type of adenovirus. Direct injection of Ad-mhcLuc and Ad-mlcLuc into the thigh muscle revealed only background luciferase activities. Conclusions: In the adenoviral system only the mlc-2v promoter may fulfil the safety requirements for a myocardial specific gene expression with a high selectivity for the ventricular myocardium, thus providing a promising tool for future **gene therapy** of cardiomyopathies.

L10 ANSWER 11 OF 11 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1992:232272 BIOSIS
DOCUMENT NUMBER: BA93:120297
TITLE: BEHAVIOR OF GENES DIRECTLY INJECTED INTO THE RAT HEART IN-VIVO.
AUTHOR(S): BUTTRICK P M; KASS A; KITSIS R N; KAPLAN M L; LEINWAND L A
CORPORATE SOURCE: DIV. CARDIOL., MONTEFIORE MED. CENT., 111 E. 210TH ST., BRONX, N.Y. 10467.
SOURCE: CIRC RES, (1992) 70 (1), 193-198.
CODEN: CIRUAL. ISSN: 0009-7330.
FILE SEGMENT: BA; OLD
LANGUAGE: English
AB Gene transfer can be achieved in the adult rat heart in vivo by direct injection of plasmid DNA. In this report we define the spatial and temporal limits of reporter gene expression after a single intracardiac injection. pRSVCAT (100 .mu.g), in which the Rous sarcoma virus long terminal repeat is fused to the chloramphenicol acetyltransferase reporter gene, and p.alpha.MHCluc (100 .mu.g), in which the .alpha.-cardiac myosin heavy chain promoter is fused to the firefly luciferase gene, were injected into hearts, and reporter gene activities were assayed at various times. Both chloramphenicol acetyltransferase and luciferase were detectable in 100% of the rats from 1 to 7 days, in 60% of the rats from 17 to 23 days, and in 30% of the rats from 38 to 60 days after injection. Reporter gene activity was largely limited to a 1-2 mm region of the ventricle surrounding the injection site. Closed circular DNA was far more effective than linear DNA in transfecting cells in vivo. The relative strengths of three different promoters, Rous sarcoma virus long terminal repeat, .**alpha.-myosin heavy chain** , and .alpha.1-antitrypsin, all fused to the luciferase reporter gene were determined. The constitutive viral promoter was .apprx.20-fold more active than the cardiac-specific cellular promoter, and the liver-specific cellular promoter was not active at all in the cardiac environment. Thus, direct injection of genes into the heart offers a simple and powerful tool with which to assess the behavior of genes in vivo. However, the potential of the technique to effect a phenotypic change in the heart is currently limited by the temporal and geographic extent of transfection.

=> s bristow m/au
L11 78 BRISTOW M/AU

=> d his

(FILE 'HOME' ENTERED AT 16:51:34 ON 30 APR 2001)

FILE 'EMBASE, BIOSIS, MEDLINE, CAPLUS, LIFESCI' ENTERED AT 16:51:48 ON 30 APR 2001
L1 1956 S ((MYOCARDIAL FAILURE) OR (MYOCARDIAL HYPERTROPHY)(50A)(TREATM
L2 1766 S ((ALPHA MYOSIN HEAVY CHAIN) OR (ALPHA-MHC))
L3 11 S L1 AND L2
L4 5 DUP REM L3 (6 DUPLICATES REMOVED)
L5 6243 S (MYOCARDIAL FAILURE) OR (MYOCARDIAL HYPERTROPHY)
L6 29 S L2 AND L5
L7 14 DUP REM L6 (15 DUPLICATES REMOVED)
L8 1 S L5 AND (GENE THERAPY) AND L2
L9 17 S L2 AND (GENE THERAPY)
L10 11 DUP REM L9 (6 DUPLICATES REMOVED)
L11 78 S BRISTOW M/AU

=> s l11 and l1
L12 0 L11 AND L1

=> s l11 and l2
L13 0 L11 AND L2

=> s l11 and l5
L14 0 L11 AND L5

=> s leinwand l/au
L15 129 LEINWAND L/AU

=> s l15 and l1
L16 0 L15 AND L1

=> s l15 and l2
L17 7 L15 AND L2

=> dup rem l17
PROCESSING COMPLETED FOR L17
L18 4 DUP REM L17 (3 DUPLICATES REMOVED)

=> d l18 1-4 ibib abs

L18 ANSWER 1 OF 4 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2001103604 EMBASE
TITLE: COOH-terminal truncated human cardiac MyBP-C alters myosin filament organization.
AUTHOR: Sebillon P.; Bonne G.; Flavigny J.; Venin S.; Rouche A.; Fiszman M.; Vikstrom K.; **Leinwand L.**; Carrier L.; Schwartz K.
CORPORATE SOURCE: P. Sebillon, Inserm Unit 523, institut de myologie, Hop. Salpetr., 47 boulevard de l'Hopital, 75651 Paris Cedex 13, France. sebillon@infobiogen.fr
SOURCE: Comptes Rendus de l'Academie des Sciences - Serie III, (2001) 324/3 (251-260).
Refs: 32
ISSN: 0764-4469 CODEN: CRASEV
COUNTRY: France
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
018 Cardiovascular Diseases and Cardiovascular Surgery
022 Human Genetics
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Myosin-binding protein C (MyBP-C) is thought to play structural and/or regulatory role in striated muscles. The cardiac isoform of MyBP-C is one of the disease genes associated with familial hypertrophic cardiomyopathy and most of the mutations produce COOH truncated proteins. In order to determine the consequences of these mutations on myosin filament

organization, we have characterized the effect of a 52-kDa NH(2)-terminal peptide of human cardiac MyBP-C on the .alpha.-**myosin heavy chain** (.alpha.-MyHC) filament organization. This peptide lacks the COOH-terminal MyHC-binding site and retains the two MyHC-binding domains located in the N-terminal part of MyBP-C. For this characterization, cDNA constructs (rat .alpha.-MyHC, full-length and truncated human cardiac MyBP-C) were transiently expressed singly or in pairwise combination in COS cells. In conformity with previous works performed on the skeletal isoform of MyBP-C, we observed that full-length cardiac MyBP-C organizes the MyHC into dense structures of uniform width. While the truncated protein is stable and can interact with MyHC in COS cells, it does not result in the same organization of sarcomeric MyHC that is seen with the full-length MyBP-C. These results suggest that the presence of truncated cardiac MyBP-C could, at least partly, disorganize the sarcomeric structure in patients with familial hypertrophic cardiomyopathy. .COPYRGT. 2001 Academie des sciences/Editions scientifiques et medicales Elsevier SAS.

L18 ANSWER 2 OF 4 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 1
ACCESSION NUMBER: 94014230 EMBASE
DOCUMENT NUMBER: 1994014230
TITLE: Cardiac .alpha.-**myosin heavy chains** differ in their induction of myocarditis. Identification of pathogenic epitopes.
AUTHOR: Liao L.; Sindhwani R.; **Leinwand L.**; Diamond B.; Factor S.
CORPORATE SOURCE: Dept. of Microbiology and Immunology, Albert Einstein College of Medicine,Bronx, NY 10461, United States
SOURCE: Journal of Clinical Investigation, (1993) 92/6 (2877-2882). ISSN: 0021-9738 CODEN: JCINAO
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
018 Cardiovascular Diseases and Cardiovascular Surgery
022 Human Genetics
026 Immunology, Serology and Transplantation
LANGUAGE: English
SUMMARY LANGUAGE: English
AB BALB/c mice develop autoimmune myocarditis after immunization with mouse cardiac myosin, whereas C57B/6 mice do not. To define the immunogenicity and pathogenicity of cardiac myosin in BALB/c mice, we immunized mice with different forms of cardiac myosin. These studies demonstrate the discordance of immunogenicity and pathogenicity of myosin heavy chains. The cardiac .alpha.- **myosin heavy chains** of BALB/c and C57B/6 mice differ by two residues that are near the junction of the head and rod in the S2 fragment of myosin. Myosin preparations from both strains are immunogenic in susceptible BALB/c as well as in nonsusceptible C57B/6 mice; however, BALB/c myosin induces a greater incidence of disease. To further delineate epitopes of myosin heavy chain responsible for immunogenicity and disease, mice were immunized with fragments of genetically engineered rat .alpha. cardiac myosin. Epitopes in the region of difference between BALB/c and C57B/6 (residues 735-1032) induce disease in both susceptible and nonsusceptible mice. The data presented here demonstrate that pathogenic epitopes of both mouse and rat myosin reside in the polymorphic region of the S2 subunit. In addition, these studies suggest that polymorphisms in the autoantigen may be part of the genetic basis for autoimmune myocarditis.

L18 ANSWER 3 OF 4 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 2
ACCESSION NUMBER: 91124786 EMBASE
DOCUMENT NUMBER: 1991124786
TITLE: Effect of aging and hypertension on myosin biochemistry and gene expression in the rat heart.
AUTHOR: Buttrick P.; Malhotra A.; Factor S.; Geenen D.; **Leinwand L.**; Scheuer J.
CORPORATE SOURCE: Department of Medicine, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY, United States
SOURCE: Circulation Research, (1991) 68/3 (645-652). ISSN: 0009-7330 CODEN: CIRUAL
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 002 Physiology
018 Cardiovascular Diseases and Cardiovascular Surgery
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The mechanisms by which the aged heart adapts to a superimposed pressure load such as hypertension have not been described. We therefore investigated biochemical and molecular genetic adaptations in the 24-month-old rat heart subjected to renovascular hypertension. Compared with 4-month-old rats, aging was associated with a 68% increase in left ventricular mass without any change in heart weight-to-body weight ratio, a 33% reduction in calcium-activated myosin ATPase activity, and a shift from a V1 to a V3 predominant myosin heavy chain (MHC) isoform distribution. A 46% reduction in .alpha.**MHC** mRNA and a reciprocal increase in .beta.-MHC mRNA was seen. When hypertension was superimposed, there was a furtber 75% increase in ventricular mass, a 63% increase in heart weight-to-body weight ratio, and a 19% reduction in myosin ATPase. Myosin isozyme distribution was further shifted to V3, and the ratio of .alpha.-**MHC** to .beta.-MHC mRNA was reduced. In addition, with hypertension a significant (>50%) reduction in the mRNA level of the cardiac sarcoplasmic reticular calcium-activated ATPase was seen. These data demonstrate that the aged myocardium is able to respond to a superimposed pressure load with a molecular genetic and protein synthetic pattern of hypertrophy analogous to that seen in younger animals.

L18 ANSWER 4 OF 4 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1991:376933 BIOSIS
DOCUMENT NUMBER: BR41:49323
TITLE: HORMONAL MODULATION OF GENES DIRECTLY INJECTED INTO THE RAT HEART.
AUTHOR(S): BUTTRICK P; KITSIS R; **LEINWAND L**
CORPORATE SOURCE: DEP. MED., ALBERT EINSTEIN COLL. MED., BRONX, NY.
SOURCE: JOINT MEETING OF THE ASSOCIATION OF AMERICAN PHYSICIANS, THE AMERICAN SOCIETY FOR CLINICAL INVESTIGATION, AND THE AMERICAN FEDERATION FOR CLINICAL RESEARCH, SEATTLE, WASHINGTON, USA, MAY 3-6, 1991. CLIN RES, (1991) 39 (2), 316A. CODEN: CLREAS. ISSN: 0009-9279.
DOCUMENT TYPE: Conference
FILE SEGMENT: BR; OLD
LANGUAGE: English

=> d his

(FILE 'HOME' ENTERED AT 16:51:34 ON 30 APR 2001)

FILE 'EMBASE, BIOSIS, MEDLINE, CAPLUS, LIFESCI' ENTERED AT 16:51:48 ON 30 APR 2001
L1 1956 S ((MYOCARDIAL FAILURE) OR (MYOCARDIAL HYPERTROPHY)(50A)(TREATM
L2 1766 S ((ALPHA MYOSIN HEAVY CHAIN) OR (ALPHA-MHC))
L3 11 S L1 AND L2
L4 5 DUP REM L3 (6 DUPLICATES REMOVED)
L5 6243 S (MYOCARDIAL FAILURE) OR (MYOCARDIAL HYPERTROPHY)
L6 29 S L2 AND L5
L7 14 DUP REM L6 (15 DUPLICATES REMOVED)
L8 1 S L5 AND (GENE THERAPY) AND L2
L9 17 S L2 AND (GENE THERAPY)
L10 11 DUP REM L9 (6 DUPLICATES REMOVED)
L11 78 S BRISTOW M/AU
L12 0 S L11 AND L1

L13 0 S L11 AND L2
L14 0 S L11 AND L5
L15 129 S LEINWAND L/AU
L16 0 S L15 AND L1
L17 7 S L15 AND L2
L18 4 DUP REM L17 (3 DUPLICATES REMOVED)

=> s l15 and l5
L19 0 L15 AND L5

=> s minobe w/au
L20 67 MINOBE W/AU

=> s l20 and l1
L21 2 L20 AND L1

=> d l21 1-2 ibib abs

L21 ANSWER 1 OF 2 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 97361878 EMBASE
DOCUMENT NUMBER: 1997361878
TITLE: Changes in gene expression in the intact human heart: Downregulation of .alpha.-myosin heavy chain in hypertrophied, failing ventricular myocardium.
AUTHOR: Lowes B.D.; **Minobe W.**; Abraham W.T.; Rizeq M.N.; Bohlmeyer T.J.; Quaife R.A.; Roden R.L.; Dutcher D.L.; Robertson A.D.; Voelkel N.F.; Badesch D.B.; Groves B.M.; Gilbert E.M.; Bristow M.R.
CORPORATE SOURCE: Dr. M.R. Bristow, Division of Cardiology, Univ. of Colorado Hlth. Sci. Center, Campus Box B139, 4200 East 9th Avenue, Denver, CO 80262, United States.
Michael.Bristow@UCHSC.edu
SOURCE: Journal of Clinical Investigation, (1997) 100/9 (2315-2324).
Refs: 67
ISSN: 0021-9738 CODEN: JCINAO
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
018 Cardiovascular Diseases and Cardiovascular Surgery
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Using quantitative RT-PCR in RNA from right ventricular (RV) endomyocardial biopsies from intact nonfailing hearts, and subjects with moderate RV failure from primary pulmonary hypertension (PPH) or idiopathic dilated cardiomyopathy (IDC), we measured expression of genes involved in regulation of contractility or hypertrophy. Gene expression was also assessed in LV (left ventricular) and RV free wall and RV endomyocardium of hearts from end-stage IDC subjects undergoing heart transplantation or from nonfailing donors. In intact failing hearts, downregulation of .beta.1-receptor mRNA and protein, upregulation of atrial natriuretic peptide mRNA expression, and increased myocyte diameter indicated similar degrees of failure and hypertrophy in the IDC and PPH phenotypes. The only molecular phenotypic difference between PPH and IDC RVs was upregulation of .beta.2-receptor gene expression in PPH but not IDC. The major new findings were that (a) both nonfailing intact and explanted human ventricular myocardium expressed substantial amounts of .alpha.-myosin heavy chain mRNA (.alpha.-MHC, 23-34% of total), and (b) in heart failure .alpha.-MHC was down-regulated (by 67-84%) and .beta.-MHC gene expression was up-regulated. We conclude that at the mRNA level nonfailing human heart expresses substantial .alpha.-MHC. In **myocardial failure** this alteration in gene expression of MHC isoforms, if translated into protein expression, would decrease myosin ATPase enzyme velocity and slow speed of contraction.

L21 ANSWER 2 OF 2 MEDLINE
ACCESSION NUMBER: 1998058665 MEDLINE
DOCUMENT NUMBER: 98058665 PubMed ID: 9410910
TITLE: Changes in gene expression in the intact human heart. Downregulation of alpha-myosin heavy chain in hypertrophied, failing ventricular myocardium.
AUTHOR: Lowes B D; **Minobe W**; Abraham W T; Rizeq M N; Bohlmeyer T J; Quaife R A; Roden R L; Dutcher D L; Robertson A D; Voelkel N F; Badesch D B; Groves B M; Gilbert E M; Bristow M R
CORPORATE SOURCE: Division of Cardiology, University of Colorado Health Sciences Center, Denver 80262, USA.
CONTRACT NUMBER: 5MO 1 RR00051 (NCRR)
HL-48013 (NHLBI)
SOURCE: JOURNAL OF CLINICAL INVESTIGATION, (1997 Nov 1) 100 (9) 2315-24.
Journal code: HS7; 7802877. ISSN: 0021-9738.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199712
ENTRY DATE: Entered STN: 19980109
Last Updated on STN: 20000303
Entered Medline: 19971223
AB Using quantitative RT-PCR in RNA from right ventricular (RV) endomyocardial biopsies from intact nonfailing hearts, and subjects with moderate RV failure from primary pulmonary hypertension (PPH) or idiopathic dilated cardiomyopathy (IDC), we measured expression of genes involved in regulation of contractility or hypertrophy. Gene expression was also assessed in LV (left ventricular) and RV free wall and RV endomyocardium of hearts from end-stage IDC subjects undergoing heart transplantation or from nonfailing donors. In intact failing hearts, downregulation of beta1-receptor mRNA and protein, upregulation of atrial natriuretic peptide mRNA expression, and increased myocyte diameter indicated similar degrees of failure and hypertrophy in the IDC and PPH phenotypes. The only molecular phenotypic difference between PPH and IDC RVs was upregulation of beta2-receptor gene expression in PPH but not IDC. The major new findings were that (a) both nonfailing intact and explanted human ventricular myocardium expressed substantial amounts of alpha-myosin heavy chain mRNA (alpha-MHC, 23-34% of total), and (b) in heart failure alpha-MHC was downregulated (by 67-84%) and beta-MHC gene expression was upregulated. We conclude that at the mRNA level nonfailing human heart expresses substantial alpha-MHC. In **myocardial failure** this alteration in gene expression of MHC isoforms, if translated into protein expression, would decrease myosin ATPase enzyme velocity and slow speed of contraction.

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L3 11 S L1 AND L2
L4 5 DUP REM L3 (6 DUPLICATES REMOVED)
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L7 14 DUP REM L6 (15 DUPLICATES REMOVED)
L8 1 S L5 AND (GENE THERAPY) AND L2
L9 17 S L2 AND (GENE THERAPY)
L10 11 DUP REM L9 (6 DUPLICATES REMOVED)
L11 78 S BRISTOW M/AU
L12 0 S L11 AND L1
L13 0 S L11 AND L2
L14 0 S L11 AND L5
L15 129 S LEINWAND L/AU
L16 0 S L15 AND L1
L17 7 S L15 AND L2
L18 4 DUP REM L17 (3 DUPLICATES REMOVED)
L19 0 S L15 AND L5
L20 67 S MINOBE W/AU
L21 2 S L20 AND L1

=> s l20 and l2
L22 2 L20 AND L2

=> d l22 1-2 ibib abs

L22 ANSWER 1 OF 2 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 97361878 EMBASE
DOCUMENT NUMBER: 1997361878
TITLE: Changes in gene expression in the intact human heart: Downregulation of .**alpha.-myosin heavy chain** in hypertrophied, failing ventricular myocardium.
AUTHOR: Lowes B.D.; **Minobe W.**; Abraham W.T.; Rizeq M.N.; Bohlmeyer T.J.; Quaife R.A.; Roden R.L.; Dutcher D.L.; Robertson A.D.; Voelkel N.F.; Badesch D.B.; Groves B.M.; Gilbert E.M.; Bristow M.R.
CORPORATE SOURCE: Dr. M.R. Bristow, Division of Cardiology, Univ. of Colorado Hlth. Sci. Center, Campus Box B139, 4200 East 9th Avenue, Denver, CO 80262, United States.
Michael.Bristow@UCHSC.edu
SOURCE: Journal of Clinical Investigation, (1997) 100/9 (2315-2324).
Refs: 67
ISSN: 0021-9738 CODEN: JCINAO
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
018 Cardiovascular Diseases and Cardiovascular Surgery
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Using quantitative RT-PCR in RNA from right ventricular (RV) endomyocardial biopsies from intact nonfailing hearts, and subjects with moderate RV failure from primary pulmonary hypertension (PPH) or idiopathic dilated cardiomyopathy (IDC), we measured expression of genes involved in regulation of contractility or hypertrophy. Gene expression was also assessed in LV (left ventricular) and RV free wall and RV endomyocardium of hearts from end-stage IDC subjects undergoing heart transplantation or from nonfailing donors. In intact failing hearts, downregulation of .beta.1-receptor mRNA and protein, upregulation of atrial natriuretic peptide mRNA expression, and increased myocyte diameter indicated similar degrees of failure and hypertrophy in the IDC and PPH phenotypes. The only molecular phenotypic difference between PPH and IDC RVs was upregulation of .beta.2-receptor gene expression in PPH but not IDC. The major new findings were that (a) both nonfailing intact and explanted human ventricular myocardium expressed substantial amounts of . **alpha.-myosin heavy chain** mRNA (. **alpha.-MHC**, 23-34% of total), and (b) in heart failure . **alpha.-MHC** was down-regulated (by 67-84%) and .beta.-MHC gene expression was up-regulated. We conclude that at the mRNA level nonfailing human heart expresses substantial .**alpha.-MHC** . In myocardial failure this alteration in gene expression of MHC isoforms, if translated into protein expression, would decrease myosin ATPase enzyme velocity and slow speed of contraction.

L22 ANSWER 2 OF 2 MEDLINE
ACCESSION NUMBER: 1998058665 MEDLINE
DOCUMENT NUMBER: 98058665 PubMed ID: 9410910
TITLE: Changes in gene expression in the intact human heart. Downregulation of **alpha-myosin heavy chain** in hypertrophied, failing ventricular myocardium.
AUTHOR: Lowes B D; **Minobe W**; Abraham W T; Rizeq M N; Bohlmeyer T J; Quaife R A; Roden R L; Dutcher D L; Robertson A D; Voelkel N F; Badesch D B; Groves B M; Gilbert E M; Bristow M R
CORPORATE SOURCE: Division of Cardiology, University of Colorado Health Sciences Center, Denver 80262, USA.
CONTRACT NUMBER: 5MO 1 RR00051 (NCRR)
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SOURCE: JOURNAL OF CLINICAL INVESTIGATION, (1997 Nov 1) 100 (9) 2315-24.
Journal code: HS7; 7802877. ISSN: 0021-9738.
PUB. COUNTRY: United States
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LANGUAGE: English
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L2 1766 S ((ALPHA MYOSIN HEAVY CHAIN) OR (ALPHA-MHC))
L3 11 S L1 AND L2
L4 5 DUP REM L3 (6 DUPLICATES REMOVED)
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L6 29 S L2 AND L5
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L8 1 S L5 AND (GENE THERAPY) AND L2
L9 17 S L2 AND (GENE THERAPY)
L10 11 DUP REM L9 (6 DUPLICATES REMOVED)
L11 78 S BRISTOW M/AU
L12 0 S L11 AND L1
L13 0 S L11 AND L2
L14 0 S L11 AND L5
L15 129 S LEINWAND L/AU
L16 0 S L15 AND L1
L17 7 S L15 AND L2
L18 4 DUP REM L17 (3 DUPLICATES REMOVED)
L19 0 S L15 AND L5
L20 67 S MINOBE W/AU
L21 2 S L20 AND L1
L22 2 S L20 AND L2

=> s l20 and l5
L23 2 L20 AND L5

=> dup rem l23
PROCESSING COMPLETED FOR L23
L24 1 DUP REM L23 (1 DUPLICATE REMOVED)

=> d l24 ibib abs

L24 ANSWER 1 OF 1 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 1
ACCESSION NUMBER: 97361878 EMBASE
DOCUMENT NUMBER: 1997361878
TITLE: Changes in gene expression in the intact human heart: Downregulation of .alpha.-myosin heavy chain in hypertrophied, failing ventricular myocardium.
AUTHOR: Lowes B.D.; **Minobe W.**; Abraham W.T.; Rizeq M.N.; Bohlmeyer T.J.; Quaife R.A.; Roden R.L.; Dutcher D.L.; Robertson A.D.; Voelkel N.F.; Badesch D.B.; Groves B.M.; Gilbert E.M.; Bristow M.R.
CORPORATE SOURCE: Dr. M.R. Bristow, Division of Cardiology, Univ. of Colorado Hlth. Sci. Center, Campus Box B139, 4200 East 9th Avenue, Denver, CO 80262, United States.
Michael.Bristow@UCHSC.edu
SOURCE: Journal of Clinical Investigation, (1997) 100/9 (2315-2324).
Refs: 67

ISSN: 0021-9738 CODEN: JCINAO
COUNTRY: United States
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018 Cardiovascular Diseases and Cardiovascular Surgery
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Using quantitative RT-PCR in RNA from right ventricular (RV) endomyocardial biopsies from intact nonfailing hearts, and subjects with moderate RV failure from primary pulmonary hypertension (PPH) or idiopathic dilated cardiomyopathy (IDC), we measured expression of genes involved in regulation of contractility or hypertrophy. Gene expression was also assessed in LV (left ventricular) and RV free wall and RV endomyocardium of hearts from end-stage IDC subjects undergoing heart transplantation or from nonfailing donors. In intact failing hearts, downregulation of .beta.1-receptor mRNA and protein, upregulation of atrial natriuretic peptide mRNA expression, and increased myocyte diameter indicated similar degrees of failure and hypertrophy in the IDC and PPH phenotypes. The only molecular phenotypic difference between PPH and IDC RVs was upregulation of .beta.2-receptor gene expression in PPH but not IDC. The major new findings were that (a) both nonfailing intact and explanted human ventricular myocardium expressed substantial amounts of .alpha.-myosin heavy chain mRNA (.alpha.-MHC, 23-34% of total), and (b) in heart failure .alpha.-MHC was down-regulated (by 67-84%) and .beta.-MHC gene expression was up-regulated. We conclude that at the mRNA level nonfailing human heart expresses substantial .alpha.-MHC. In **myocardial failure** this alteration in gene expression of MHC isoforms, if translated into protein expression, would decrease myosin ATPase enzyme velocity and slow speed of contraction.

=> s nakao k/au
L25 3636 NAKAO K/AU

=> s l25 and l1
L26 0 L25 AND L1

=> s l25 and l2
L27 2 L25 AND L2

=> dup rem l27
PROCESSING COMPLETED FOR L27
L28 1 DUP REM L27 (1 DUPLICATE REMOVED)

=> d l28 ibib abs

L28 ANSWER 1 OF 1 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 1
ACCESSION NUMBER: 97135846 EMBASE
DOCUMENT NUMBER: 1997135846
TITLE: Altered expression of atrial natriuretic peptide and contractile protein genes in hypertrophied ventricle of JVS mice with systemic carnitine deficiency.
AUTHOR: Yoshimine K.; Horiuchi M.; Suzuki S.; Kobayashi K.; Abdul J.M.; Masuda M.; Tomomura M.; Ogawa Y.; Itoh H.; **Nakao** K.; Osame M.; Saheki T.
CORPORATE SOURCE: M. Horiuchi, Department of Biochemistry, Faculty of Medicine, Kagoshima University, 8-35-1 Sakuragaoka, Kagoshima 890, Japan.
SOURCE: Journal of Molecular and Cellular Cardiology, (1997) 29/2 (571-578).
Refs: 47
ISSN: 0022-2828 CODEN: JMCDAY
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
018 Cardiovascular Diseases and Cardiovascular Surgery
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
AB To characterize cardiac hypertrophy in juvenile visceral steatosis (JVS) mice with systemic carnitine deficiency, we investigated how the hypertrophy develops and whether it is associated with altered expression of any specific genes, especially atrial natriuretic peptide (ANP) and contractile protein genes, in the hypertrophied ventricle. Cardiac hypertrophy in JVS mice became apparent at 10 days after birth and progressed during development. The hypertrophy was observed in the ventricles but not in the atria. ANP mRNA was more intensively expressed in JVS ventricles than in control even at 5 days. Carnitine administration ameliorated the cardiac hypertrophy and suppressed the augmentation of ANP mRNA in the ventricles. Isoform change of expression of .alpha.-actin genes from cardiac to skeletal was seen in the ventricles of JVS mice at 2 weeks. There was no difference in the ratio of .beta.-myosin heavy chain mRNA to **.alpha.-myosin heavy chain** mRNA between control and JVS mice at 5 days, but at 2 weeks the ratio was significantly lower in JVS mice than in control. These results suggest that the molecular characteristics of cardiac hypertrophy caused by carnitine deficiency are different from those of cardiac hypertrophy caused by aortic constriction.

=> s l25 and l5
L29 8 L25 AND L5

=> dup rem l29
PROCESSING COMPLETED FOR L29
L30 3 DUP REM L29 (5 DUPLICATES REMOVED)

=> d his

(FILE 'HOME' ENTERED AT 16:51:34 ON 30 APR 2001)

FILE 'EMBASE, BIOSIS, MEDLINE, CAPLUS, LIFESCI' ENTERED AT 16:51:48 ON 30 APR 2001
L1 1956 S ((MYOCARDIAL FAILURE) OR (MYOCARDIAL HYPERTROPHY)(50A)(TREATM
L2 1766 S ((ALPHA MYOSIN HEAVY CHAIN) OR (ALPHA-MHC))
L3 11 S L1 AND L2
L4 5 DUP REM L3 (6 DUPLICATES REMOVED)
L5 6243 S (MYOCARDIAL FAILURE) OR (MYOCARDIAL HYPERTROPHY)
L6 29 S L2 AND L5
L7 14 DUP REM L6 (15 DUPLICATES REMOVED)
L8 1 S L5 AND (GENE THERAPY) AND L2
L9 17 S L2 AND (GENE THERAPY)
L10 11 DUP REM L9 (6 DUPLICATES REMOVED)
L11 78 S BRISTOW M/AU
L12 0 S L11 AND L1
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L17 7 S L15 AND L2
L18 4 DUP REM L17 (3 DUPLICATES REMOVED)
L19 0 S L15 AND L5
L20 67 S MINOBE W/AU
L21 2 S L20 AND L1
L22 2 S L20 AND L2
L23 2 S L20 AND L5
L24 1 DUP REM L23 (1 DUPLICATE REMOVED)
L25 3636 S NAKAO K/AU
L26 0 S L25 AND L1
L27 2 S L25 AND L2
L28 1 DUP REM L27 (1 DUPLICATE REMOVED)
L29 8 S L25 AND L5
L30 3 DUP REM L29 (5 DUPLICATES REMOVED)

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---Logging off of STN---

=>
Executing the logoff script...

=> LOG Y

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TOTAL

	ENTRY	SESSION
CA SUBSCRIBER PRICE	-7.64	-7.64

STN INTERNATIONAL LOGOFF AT 17:00:45 ON 30 APR 2001